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Secondary Deuterium Isotope Effects for Certain Acyl Transfer Reactions of Phenyl Formates[1a]

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Abstract: Kinetic α secondary deuterium isotope effects, k_D/k_H, for formyl group transfer from either the 4-methoxyphenyl or 4-nitrophenyl esters, or both, of formic and deuterioformic acids to a variety of oxygen acceptors have been measured at 25 °C in aqueous solution: hydroperoxide ion, 1.12; 2-propynol anion, 1.13; hexafluoropropan-2-ol anion, 1.14; and water, 1.22. In addition, corresponding isotope effects have been obtained for general-base-catalyzed formyl group transfer from the same substrates to acetate, 1.21, formate, 1.23, and trimethylamine *N*-oxide, 1.20. The α secondary deuterium isotope effect for acid-catalyzed hydrolysis of both esters has been determined to be 1.24. These data are interpreted to reflect considerable, and perhaps complete, carbon–oxygen bond formation in the transition state for addition of oxygen nucleophiles to phenyl formates. Finally, corresponding isotope effects were determined for reaction of fluoride, 1.19, and azide, 1.14, which also suggest substantial covalent bond formation between ester and nucleophile in the transition state.

Addition of nucleophilic reagents to the acyl carbon atom, as in the hydrolysis and aminolysis of esters, will result in progressive rehybridization of the acyl carbon atom of the substrate from sp^2 to sp^3, corresponding to formation of a tetrahedral addition intermediate, and then from sp^3 to sp^2, as the tetrahedral species decomposes to products. Should the reaction occur without formation of a tetrahedral intermediate, a related type of rehybridization should occur, although sp^3 geometry will not be fully attained at any stage along the reaction coordinate. Since the magnitude of kinetic α secondary deuterium isotope effects is largely determined by changes in the frequency of the out of plane bending mode which accompanies sp^2-sp^3 rehybridization,[2,3] it follows that measurements of such effects should yield useful information concerning transition-state structures for acyl transfer reactions of formic acid derivatives.

Bilkadi et al. have, in fact, pursued such measurements for hydrolysis and hydrazinolysis of methyl and ethyl formates and were able to define the transition state for these reactions in considerable detail,[4] particularly for those reactions for which oxygen-18 isotope effects had also been measured.[5] In the work described herein, we have elected to examine α secondary deuterium isotope effects for acyl transfer reactions of phenyl formates. This system offers the possibilities of (1) ready modification of substrate reactivity through change of polar substituents in the leaving group, (2) examination of a large number of nucleophilic reagents which react with these esters at convenient rates, and (3) correlation of the results with those in the extensive literature for acyl transfer reactions of phenyl acetates.[6-8] Results reported herein, the first phase of anticipated studies, deal mainly with reactions of oxy anions with 4-methoxyphenyl and 4-nitrophenyl formates.

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Experimental Section

Materials. Sodium formate-1-*d* was prepared from sodium cyanide and deuterium oxide by an adaptation of a published procedure.[9] Powdered sodium cyanide was dried in vacuo in a drying pistol at 150 °C for 2 h employing sodium hydroxide as desiccant. Dried sodium cyanide (122 g) was transferred to a flask and dissolved in 170 mL of deuterium oxide; this solution was refluxed under nitrogen for 6 days. Most of the remaining deuterium oxide was removed by distillation, 250 mL of 85% phosphoric acid added, and a formic acid-1-*d*/water mixture removed by distillation in vacuo. The entire distillate was neutralized with sodium hydroxide and most of the water was removed by heating. Sodium formate-1-*d* was precipitated by addition of ethanol, collected by filtration, washed with ethanol, and dried at 120 °C, yield 113 g, 66% based on sodium cyanide.

Anhydrous formic acid-1-*d* was obtained by distillation in vacuo at 30 °C of a slurry of 32 g of dry sodium formate-1-*d* and 88 g of anhydrous phosphoric acid, prepared from 85% phosphoric acid and P_2O_5, yield 15.7 g of formic acid-1-*d*, 72% based on sodium formate. Alternatively, anhydrous formic acid-1-*d* was purchased from the Merck Chemical Co.

4-Methoxyphenyl formate and 4-nitrophenyl formate and the corresponding esters derived from formic acid-1-*d* were synthesized from formic acetic anhydride[10] or formic-1-*d* acetic anhydride and the appropriate phenol according to a published procedure.[11] The 4-nitrophenyl formate crystallized during the reaction, the crystals were collected by filtration, and the products were recrystallized from carbon tetrachloride. The isolated yield was 43% of theoretical based on 4-nitrophenol. Crystallization of 4-methoxyphenyl formate was induced by cooling the reaction mixture following removal of excess acetic acid and formic acetic anhydride by evaporation in vacuo. The product was collected and purified as described for the 4-nitro compound; isolated yield was 54% based on 4-methoxyphenol. Treatment of each ester with base in aqueous solution produced a yield of 100 ± 2% of 4-nitrophenolate ion based on spectrophotometric analysis at 409 nm. ^1H NMR spectra of the two deuterio esters present as concentrated esters in carbon tetrachloride or deuteriochloroform revealed no detectable resonance for the hydrogen on acyl carbon. We estimate that a 3% contamination of the deuterio esters with the corresponding protio compounds would have been detected in these measurements. Consequently, the isotopic purity of the deuterio esters is not less than 97%.

Trimethylamine *N*-oxide was prepared by oxidation of trimethylamine as previously described.[12] Other reagents employed in this study were obtained commercially and either redistilled or recrystallized prior to use. Glass-distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically employing a Zeiss PMQ II spectrophotometer equipped with a cell holder through which was circulated water from a carefully thermostated bath. Nucleophilic reactions of 4-methoxyphenyl formate and formate-1-*d* were monitored by observing phenol appearance at 292 nm; initial ester concentration was 3.8×10^{-4} M and each solution contained 1% dioxane. Reactions of 4-nitrophenyl formate and formate-1-*d* were following by observing phenol appearance at 320 nm; initial ester concentration was 1×10^{-4} M and each solution contained 1% acetonitrile. All reactions were carried out at ionic strength 1.0, maintained with KCl, and at 25 °C.

Individual rate constants were obtained from nonlinear regression analysis of 100-200 data points as previously described.[13] Secondary deuterium isotope effects were usually measured employing a single concentration of nucleophilic reagent; more than one concentration was employed in several cases specified below. In each case, measurements were made in triplicate, alternating protio and deuterio substrates in the kinetic measurements to reduce systematic errors. Isotope effects were ordinarily reproducible to within ±0.01.

Results

Rate constants for acidic, neutral, and alkaline hydrolysis of 4-nitrophenyl and 4-methoxyphenyl formate in aqueous solution at 25 °C and ionic strength 0.5 are collected in Table I. Note that the rate of acid-catalyzed hydrolysis is much less sensitive to the nature of the polar substituent than are those for the pH-independent and base-catalyzed reactions. Using just the data points for the 4-nitro and 4-methoxy esters and assuming that the rate constants are correlated by the σ substituent constants, the following approximate values of ρ have been derived: k_H, 0.2; k_0, 1.5; k_{OH}, 1.5. These values may be slightly too high since there is considerable evidence to indicate that rate constants for reactions of 4-nitrophenyl esters are best correlated with those for corresponding esters bearing other substituents if a σ value for *p*-nitro somewhat more positive than the standard value of 0.778 is used.[14,15] By way of comparison, the hydroxide ion catalyzed hydrolysis of the phenyl esters of several benzoic acids has a value of ρ near 1.23;[15] and acid-catalyzed hydrolysis of phenyl acetates in 60% acetone has a value of ρ near −0.2.[16]

Table I. Second-Order Rate Constants for Acidic, Neutral, and Alkaline Hydrolysis of 4-Nitrophenyl and 4-Methoxyphenyl Formates in Aqueous Solution at 25 °C and Ionic Strength 0.5

substrate	k_H, M^{-1} min^{-1}	k_0, M^{-1} min^{-1}	k_{OH}, M^{-1} min^{-1}
4-nitro	0.35	6.9×10^{-4}	1.2×10^6
4-methoxy	0.237	2.04×10^{-5}	4.0×10^4

The second-order rate constant for the base-catalyzed hydrolysis of the phenyl formates, which may reflect general base catalysis of water attack,[17] is 2 to 5 × 10^9 greater than the corresponding constant for the pH-independent reaction (Table I). This ratio is similar to that observed for the same reactions of phenyl acetate and 4-nitrophenyl acetate, and somewhat greater than that observed for 2,4-dinitrophenyl acetate.[6] The ratio is much greater than that observed for attack of hydroxide ion and water on stable organic cations.[17]

The half-life for neutral hydrolysis of 4-methoxyphenyl formate is near 620 min while that for the corresponding 4-nitro derivative is only 20 min at 25 °C and ionic strength 0.50. Since our methodology for measurement of secondary deuterium isotope effects depends on collection by hand of a large number of data points, the former substrate is the more suitable of the two for our studies and the bulk of the measurements have been done with it. Employing this substrate, it was generally possible to choose a single concentration of a nucleophilic reagent so that two conditions were satisfied: (1) more than 90% of the rate of disappearance of ester could be attributed to reaction with the nucleophile of interest; and (2) the reaction proceeded at a rate consistent with making the necessary number of experimental measurements. Consequently isotope effects reported for this substrate were uniformly measured in at least triplicate at a single nucleophile concentration. The two conditions noted above cannot be simultaneously satisfied for 4-nitrophenyl formate employing our methodology. Consequently, secondary deuterium isotope effects for reactions of this substrate were calculated from the relative slopes of plots of first-order rate constants against the concentration of nucleophile for the protio and deuterio species. In one case (see Table II), secondary deuterium isotope effects were measured for the same reaction employing the two methods and identical results, within experimental uncertainty, were obtained.

In Table II are collected secondary deuterium isotope effects for reactions of 4-methoxyphenyl and 4-nitrophenyl formate with a number of nucleophilic reagents. In all cases in which a single nucleophile concentration was employed, it was assured that more than 90% of the reaction proceeded with the nucleophile through comparison of the observed rate with that calculated on the basis of acidic, neutral, and alkaline hydrolysis, employing the rate constants in Table I.

In the course of measurement of secondary deuterium isotope effects, several second-order rate constants for reaction of the substituted phenyl formates with oxy anions were obtained. These are collected in Table III.

Discussion

Reactions with Oxygen Anions. The mechanism of addition

Table II. Secondary Deuterium Isotope Effects for Reactions of Substituted Phenyl Formates with Several Nucleophilic Reagents[a]

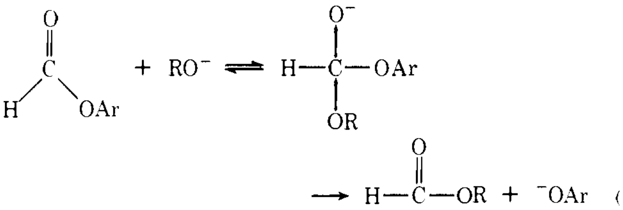
nucleophile	pK_a[b]	pH	concn total, M	concn free base,[c] M	f_r[d]	substituent 4-methoxy	 4-nitro
acetate[e]	4.76	6.04, 4.98	3.38, 0.045–0.45	3.21, 0.03–0.29	0.96, 1.0	1.212 ± 0.003	1.20 ± 0.01
formate	3.75	3.61	0.04–0.45	0.03–0.19	1.0		1.23 ± 0.01
trimethylamine *N*-oxide[e]	4.60	6.28, 4.80	1.0, 0.07–0.30	0.98, 0.05–0.19	0.93, 1.0	1.198 ± 0.004	1.22 ± 0.01
hydroperoxide anion	11.6	4.40	0.135	8.5×10^{-9}	0.95	1.119 ± 0.007	
2-propynol anion	13.5	6.40	0.847	6.0×10^{-9}	0.94	1.130 ± 0.012	
hexafluoropropan-2-ol anion	9.3	6.33	0.76	8.1×10^{-5}	0.95	1.141 ± 0.014	
water[e]	15.74	3.33, 1.4–2.7	55	55	1.0, 1.0	1.222 ± 0.007	1.22 ± 0.01
fluoride	4.18	4.0	4.0	2.4	0.96	1.192 ± 0.038	
azide	– 4.72	4.10	0.09	0.05	0.93	1.137 ± 0.003	
hydrated proton[e]	−1.74	0.65, 0.70	0.22, 0.20		0.98, 0.67	1.246 ± 0.007	1.24 ± 0.01

[a] All α secondary deuterium isotope effects are expressed as k_D/k_H. [b] Taken from W. P. Jencks in "Handbook of Biochemistry", 2nd ed., H. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1973, p J150. [c] Calculated from the observed pH, tabulated pK_a, and the Henderson–Hasselbalch equation. [d] Fraction of total rate of disappearance of ester due to reaction with indicated nucleophilic reagent. Calculated as described in the text. [e] The first values of pH, concentration, and f_r refer to measurements made with the 4-nitrophenyl ester; the second values refer to measurements made with the 4-methoxyphenyl ester.

Table III. Second-Order Rate Constants for Reaction of 4-Nitrophenyl or 4-Methoxyphenyl Formate with Several Oxy Anions at 25 °C and Ionic Strength 0.50

nucleophilic reagent	k_2, $M^{-1}\,min^{-1}$ 4-nitro	 4-methoxy
acetate	0.76	0.014
formate	0.15	
trimethylamine *N*-oxide	0.36	
$(CF_3)_2CHO^-$		304
HOO^-		5.8×10^6
$HC{\equiv}CCH_2O^-$		5.5×10^5

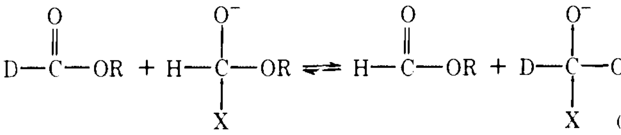
of nucleophilic reagents is considered to involve a two-step mechanism which may be complicated by proton transfer reactions.[6-8,18-20] Among these reactions, those involving the attack of oxy anions on esters such as phenyl formates should be particularly simple (eq 1). Because of the symmetry of these



(1)

reactions with respect to the nature of the entering and leaving groups, it has been convincingly argued that the transition state should resemble reactants if the nucleophile is more basic than the leaving group and, conversely, resemble products if the leaving group is more basic than the nucleophile.[6] These arguments follow irrespective of whether or not a tetrahedral addition compound having a significant lifetime is formed as a reaction intermediate. If such an intermediate is formed, then its formation should be rate determining for nucleophiles more basic than the leaving group and, conversely, its decomposition to products should be rate determining for less basic nucleophiles.

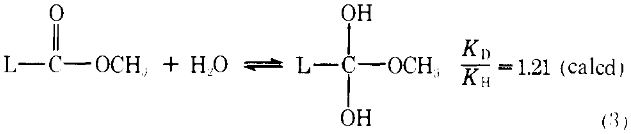
Interpretation of the secondary deuterium isotope effects can be made on a comparative basis, i.e., a change in isotope effect with change in nucleophile yields evidence concerning the dependence of transition-state structure on nucleophile structure, or on an absolute basis, in which attempts are made to interpret isotope effects in terms of bond orders in the transition state. Successful use of the latter approach, which involves assumptions noted later at any event, requires that the equilibrium isotope effect for complete rehybridization from sp^2 to sp^3, corresponding to the maximum observable kinetic isotope effect, be known. This is equivalent to knowing the value of K_D/K_H for the equilibrium[4] of eq 2. Since no direct



$$\mathrm{D{-}\overset{O}{\overset{\|}{C}}{-}OR + H{-}\underset{X}{\overset{O^-}{C}}{-}OR \rightleftharpoons H{-}\overset{O}{\overset{\|}{C}}{-}OR + D{-}\underset{X}{\overset{O^-}{C}}{-}OR} \quad (2)$$

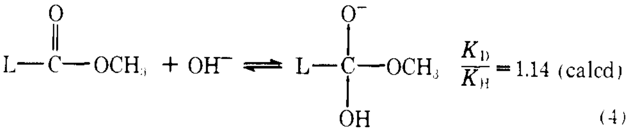
experimental determination of this value is convenient, one must rely on indirect estimates. As is detailed below, the resulting estimates of equilibrium α secondary deuterium isotope effects differ quite significantly.

Bilkadi et al. have made a simple calculation of the equilibrium α secondary deuterium isotope effect for addition of water to methyl formate[4] (eq 3) employing a few vibrational



$$\mathrm{L{-}\overset{O}{\overset{\|}{C}}{-}OCH_3 + H_2O \rightleftharpoons L{-}\underset{OH}{\overset{OH}{C}}{-}OCH_3} \quad \frac{K_D}{K_H} = 1.21\ \text{(calcd)} \quad (3)$$

frequencies for model compounds and the Streitwieser equation.[2] From the value of K_D/K_H of 1.21 obtained for the formation of the neutral tetrahedral intermediate (eq 3), a limiting value of 1.14 was obtained for the kinetic isotope effect for addition of hydroxide ion to methyl formate (eq 4).

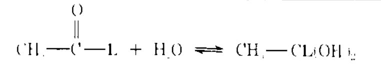
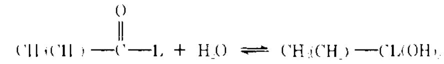
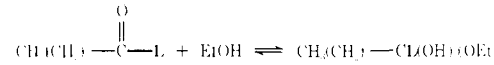
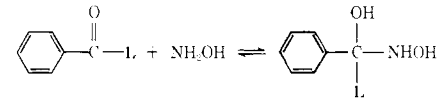
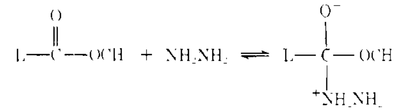
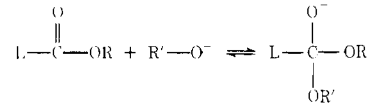


$$\mathrm{L{-}\overset{O}{\overset{\|}{C}}{-}OCH_3 + OH^- \rightleftharpoons L{-}\underset{OH}{\overset{O^-}{C}}{-}OCH_3} \quad \frac{K_D}{K_H} = 1.14\ \text{(calcd)} \quad (4)$$

Subsequently, a more detailed calculation, based on the complete Bigeleisen equation[21] and employing a detailed force-field analysis,[22] has been carried out:[23] a value of K_D/K_H for formation of the neutral tetrahedral intermediate (eq 3) of 1.23 was obtained from which a value of the same ratio for formation of the anionic tetrahedral intermediate of 1.16 may be calculated.[4] These values are in accord with those obtained earlier.

Considerations based on measured equilibrium isotope effects for related reactions suggest that the calculated values indicated above may be substantially too small. A collection of pertinent data is contained in Table IV. The first point to recognize is that the equilibrium isotope effects for addition of oxygen and nitrogen nucleophiles to aldehydes are essentially the same; compare the first three entries in Table IV with the fourth one. It follows that the equilibrium isotope effects for addition of nitrogen and oxygen nucleophiles to esters

Table IV. A Collection of Equilibrium α Secondary Deuterium Isotope Effects for Addition of Nucleophilic Reagents to Carbonyl and Acyl Carbon Atoms

reaction	K_D/K_H	ref
 $\mathrm{CH_3{-}\overset{O}{\overset{\Vert}{C}}{-}L + H_2O \rightleftharpoons CH_3{-}CL(OH)_2}$	1.37	*a*
 $\mathrm{CH_3(CH_2)_2{-}\overset{O}{\overset{\Vert}{C}}{-}L + H_2O \rightleftharpoons CH_3(CH_2)_2{-}CL(OH)_2}$	1.39	*b*
 $\mathrm{CH_3(CH_2)_2{-}\overset{O}{\overset{\Vert}{C}}{-}L + EtOH \rightleftharpoons CH_3(CH_2)_2{-}CL(OH)(OEt)}$	1.37	*b*
	1.36	*c*
 $\mathrm{L{-}\overset{O}{\overset{\Vert}{C}}{-}OCH + NH_2NH_2 \rightleftharpoons L{-}\underset{{}^{+}NH_2NH_2}{\overset{O^-}{C}}{-}OCH}$	1.35-1.38	4
 $\mathrm{L{-}\overset{O}{\overset{\Vert}{C}}{-}OR + R'{-}O^- \rightleftharpoons L{-}\underset{OR'}{\overset{O^-}{C}}{-}OR}$	1.15, 1.30	*d*

[a] R. Wolfenden, personal communication. [b] E. A. Hill and S. A. Milosevich, *Tetrahedron Lett.*, 4553 (1976). [c] L. do Amaral, M. P. Bastos, H. G. Bull, and E. H. Cordes, *J. Am. Chem. Soc.*, **95**, 7369 (1973). [d] Values based on force field calculations or comparison with the data contained in this table, as explained in the text.

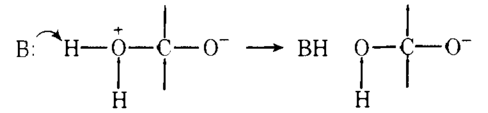
should also be about the same. Bilkadi et al. have neatly provided the limiting secondary deuterium isotope effect for addition of hydrazine to methyl formate, the fifth entry in Table IV, by determining the kinetic isotope effect under conditions in which abstraction of a proton from the tetrahedral intermediate is rate determining.[4,24] This value is in the range $K_D/K_H = 1.35-1.38$. Assuming that the secondary deuterium isotope effect on formation of a zwitterionic tetrahedral intermediate is about the same as that for formation of the neutral adduct,[25] it follows that the limiting isotope effect for formation of the neutral tetrahedral intermediate shown in eq 3 should be in this range and, therefore, that the limiting isotope effect for addition of an oxy anion to an ester (eq 4) should be near 1.30.

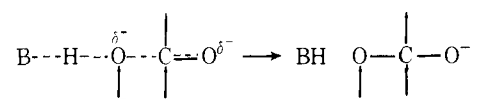
Since it is not possible to reliably measure a limiting kinetic isotope effect for addition of oxy anions to phenyl formates and since the two approaches just described yield quite different results, we shall proceed by interpreting our data on the basis of two values for K_D/K_H: one near 1.15 based on force-field calculations and one near 1.30 based on comparisons with related data.

Secondary deuterium isotope effects for reaction of six oxy anions with 4-methoxyphenyl formate fall into two classes. In the first are three moderately basic species (HOO^-, $HC{\equiv}CCH_2O^-$, and $(CF_3)_2CHO^-$), for which the isotope effects fall in the range 1.12-1.14. On the basis of the value of 1.15 for the limiting isotope effect for oxy anion addition to esters, one would conclude that the transition state for these reactions is nearly tetrahedral. In contrast, employing the value of 1.30, one concludes that the transition states are "intermediate," with the carbonyl carbon atom having a geometry about midway between trigonal and tetrahedral.[26]

Into the second class fall the isotope effects for reaction of the three weakly basic oxy anions (acetate, formate, and trimethylamine *N*-oxide). In this case, the isotope effects range from 1.20 to 1.23.

The behavior of these weakly basic nucleophiles in other systems strongly suggests that their reactions with phenyl formates involve general base catalysis of the attack of water rather than direct nucleophilic attack.[27] This point of view is supported by the observation that the second-order rate constants for reaction of these nucleophiles and water with 4-nitrophenyl formate (Tables I and III) are correlated with values for the pK_a of the conjugate acids by a line having a Brønsted β value of 0.44 (plot not shown). This value is close to that previously determined for general-base-catalyzed attack of water on ethyl dichloroacetate.[28] Were direct nucleophilic attack involved, the lower value for the limiting isotope effect would of necessity be incorrect since the kinetic value cannot be greater than the equilibrium one. The limiting value for general-base-catalyzed addition of water will depend on the mechanism of the catalysis. If the slow step is the abstraction of a proton from a zwitterionic tetrahedral addition intermediate (eq 5) the limiting value might approach that for formation of the neutral tetrahedral intermediate, 1.35-1.38 according to the upper estimate or 1.21-1.23 according to the lower one. On the other hand, proton abstraction concerted with covalent bond formation (eq 6) might yield a value ranging from unity to that for formation of the anionic tetrahedral intermediate, 1.30 or 1.15.[4] Thus, if the lower limiting value is correct or nearly so, one must conclude that the reaction is stepwise and involves rate-determining proton transfer (eq 5). If the upper limiting value is more nearly accurate, then the transition state would again be "intermediate" and the reaction is concerted (eq 6).


$$\mathrm{B{:}\ H{-}\underset{H}{\overset{+}{O}}{-}\overset{|}{\underset{|}{C}}{-}O^-} \longrightarrow \mathrm{BH\ \ \underset{H}{O}{-}\overset{|}{\underset{|}{C}}{-}O^-} \qquad (5)$$


$$\mathrm{B{-}{-}{-}H{-}{-}{-}\underset{H}{\overset{\delta^-}{O}}{-}{-}{-}\overset{|}{\underset{|}{C}}{=}{-}O^{\delta^-}} \longrightarrow \mathrm{BH\ \ \underset{H}{O}{-}\overset{|}{\underset{|}{C}}{-}O^-} \qquad (6)$$

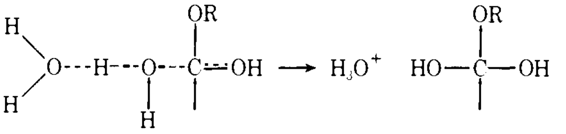
There are three lines of experimental evidence which bear on the questions of interpretation of the α secondary deuterium isotope effects raised above. First, a careful analysis of structure-reactivity correlations for addition of alkoxide ions to phenyl acetates strongly suggests that the transition state has considerable negative charge on the attacking group.[29] That is, carbon-oxygen bond formation is by no means complete when the transition-state geometry is reached. This conclusion is consistent with interpretation of our data provided that one assumes that the limiting isotope effect is near 1.30.

Second, kinetic β secondary deuterium isotope effects for base-catalyzed hydrolysis of esters and acetanilides also suggest transition states for these reactions in which the transition-state geometry is intermediate between trigonal and tetrahedral. For the attack of hydroxide ion on ethyl acetate[30] and on *p*-nitrophenylacetanilide[31] the kinetic isotope effects are significantly nearer unity than is the limiting equilibrium isotope effect.[32] In addition, the kinetic isotope effect for addition of bisulfite to methyl ketones is smaller than that for the corresponding equilibrium.[33,34]

Third, the α secondary deuterium isotope effects for attack of hydroxide ion on methyl formate and ethyl formate are 1.05 and 1.10, respectively.[4] These values are considerably less than either estimate for the limiting equilibrium isotope effect and suggest early to intermediate transition states.

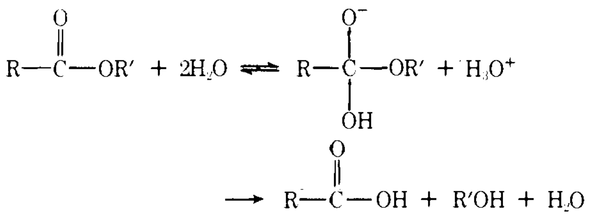
In sum, one cannot be certain of the meaning of the α secondary deuterium isotope effects for oxy anion attack of phenyl formates reported herein in terms of precise transition state structures. However, the bulk of the evidence suggests that these transition states have significant but incomplete carbon-oxygen bond formation. That is, on balance, the available evidence is more nearly consistent with a limiting isotope effect of 1.30 for these reactions. This has the consequence of favoring a concerted mechanism for general-base-catalyzed addition of water to phenyl formates.

Acid-Catalyzed Hydrolysis. Acidic hydrolysis of both 4-methoxyphenyl and 4-nitrophenyl formates occurs with a secondary deuterium isotope effect near 1.24 (Table II). This value is essentially identical with that previously measured for the acid-catalyzed hydrolysis of both methyl and ethyl formates.[4] Although the subject of continuing investigation and debate,[35] acid-catalyzed hydrolysis of most esters is considered to proceed via preequilibrium protonation of the substrate followed by rate-determining attack of water assisted by another water molecule[36,37] (eq 7). Since this mechanism leads directly to the neutral tetrahedral addition intermediate, a maximal isotope effect of 1.21–1.23 or 1.35–1.38 would be expected, as noted above. If the lower limit applies, it follows that carbon–oxygen bond formation must be complete or nearly so in the transition state. The upper limit would require a transition state having incomplete C–O bond formation.



$$\mathrm{H_2O\cdots H\cdots O(H)\cdots C(OR)(\!=\!OH)} \longrightarrow \mathrm{H_3O^+} \quad \mathrm{HO{-}C(OR){-}OH} \qquad (7)$$

pH-Independent Hydrolysis. The recent and detailed studies of Kurz and co-workers strongly suggest that the pH-independent hydrolysis of esters occurs via the following pathway[35,37–39] (eq 8). Although both steps may contribute to the overall rate of the reaction, the rate constant for hydrolysis is generally greater than that for oxygen-18 exchange, suggesting that the first step may be rate determining. Since this yields the anionic tetrahedral intermediate, we expect a maximal secondary deuterium isotope effect near 1.15 or 1.30. The lower limit is clearly inconsistent with the measured isotope effect of 1.22, constituting an additional line of evidence that the upper limit for the isotope effect is the more nearly correct of the two. Adopting this point of view, the measured isotope effect requires that tetrahedral geometry is approached but not attained in the transition state for the pH-independent hydrolysis of phenyl formates.



$$\mathrm{R{-}C({=}O){-}OR' + 2H_2O \rightleftharpoons R{-}C(O^-)(OH){-}OR' + H_3O^+ \longrightarrow R{-}C({=}O){-}OH + R'OH + H_2O} \qquad (8)$$

Inorganic Ions. Secondary deuterium isotope effects for reaction of 4-methoxyphenyl formate with fluoride, 1.19, and azide, 1.14, have been measured (Table II). Although a precise interpretation of these isotope effects must await determination of limiting values for formation of tetrahedral adducts, it is clear that the transition states must contain considerable tetrahedral character.

Substrate Structure. In four cases (Table II), secondary deuterium isotope effects for reactions of the same nucleophile with both the 4-methoxy- and 4-nitrophenyl formates have been measured. In no case is the difference beyond experimental error. These results suggest that the transition-state structure for the indicated reactions is not strongly dependent on the reactivity of the substrate.

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References and Notes

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(26) The interpretations of secondary deuterium isotope effects indicated in this paper are based on the reasonable assumption that these change in an approximately linearly way with changes in bond order in the transition state. Drs. John Hogg and R. S. Schowen have calculated α secondary deuterium isotope effects for acetaldehyde hydration as a function of transition state bond order and obtain a result which accords with this assumption (J. Hogg, Ph.D. Thesis, Kansas University, 1975).

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